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Simple and Efficient Synthesis of Substituted 2-Pyrrolidinones, 2-Pyrrolones, and Pyrrolidines from Enaminones of Baylis−Hillman Derivatives of 3-Isoxazolecarbaldehydes[§,‡]

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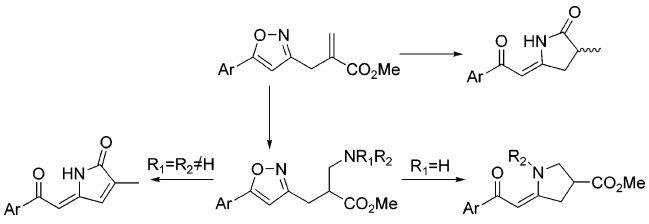

The enaminones, generated from derivatives of appropriately substituted Baylis−Hillman adducts of 3-isoxazolecarbaldehydes, undergo intramolecular ring-closure reactions to afford substituted 2-pyrrolidinones, 1,5-dihydro-2-pyrrolones, and *N*-substituted pyrrolidines in good yields.

The five-membered nitrogen-containing heterocycles are ubiquitously present in natural products and are components of several compounds with medicinal properties. Among these heterocycles 2-pyrrolidinone, pyrrolone, and pyrrolidine have special significance because they represent an integral part of different alkaloids and toxins such as epolactaene,[1] preussin,[2] cylindricine,[3] lepadiformine,[4] etc. A few of the recently reported examples of 2-pyrrolidinone and pyrrolidine derivatives exhibiting promising bioactivity are Piracetam as a nootropic,[5] Levetiracetam and its analogues as an antiepileptic,[6−8] 8-aza-11-deoxyPGE$_1$ [9] as an EP$_4$ agonist, DM 232 as a cognition enhancer,[10] and 3,5-disubstituted-2-pyrrolidinones as inhibitors of collagen-induced thrombocyte aggregation for treatment of inflammation.[11] In light of these observations, the interest and need for simple and efficient synthesis of pyrrolidinone and pyrrolidine derivatives exists.

The facile cleavage of the N−O bond experienced by the isoxazole nucleus under simple reaction conditions makes it an important synthetic intermediate for the construction of arrays of molecular assemblies including different heterocycles and natural products.[12] As a part of our ongoing research program for studying the synthetic utility of the isoxazole derivatives, obtained as products of Baylis−Hillman reaction of different isoxazolecarbaldehydes,[13] we envisioned the synthesis of 2-pyrrolidinones from derivatives of the Baylis−Hillman adducts of 3-isoxazolecarbaldehydes. The details of this study are presented here.

During the studies on the synthesis of the corrin frameworks, Stevens[14] reported that an appropriately substituted isoxazole derivative upon hydrogenolysis led to the formation of the 2-pyrrolidinone derivative. Similarly, Jones et al.[15] reported that the appropriately substituted isoxazole derivative under Pd/C-promoted hydrogenation affords the 2-pyrrolidinone derivative in good yield, but both these reports dealt with only limited substrates. On the basis of these reports, we have reasoned that derivatives of the Baylis−Hillman adduct, obtained by reacting substituted 3-isoxazolecarbaldehydes with acrylates, upon hydrogenolysis, would lead to enaminones which could undergo intramolecular cyclization involving the amino and the ester groups to yield substituted 2-pyrrolidinone derivatives. However, during the detailed catalytic hydrogenation studies of Baylis−Hillman derivatives reported recently by us we were unsuccessful in this direction.[16] Attempts with the Pd/C-promoted hydrogenolysis followed by cyclization as reported by Jones et al. also failed to work with these derivatives. However, this impediment has now been removed by carrying out Raney-Ni-promoted hydrogenolyses of Baylis−Hillman derivatives **4a**−**e** and **5a**−**e**. The synthesis of starting substrates (**4a**−**e** and

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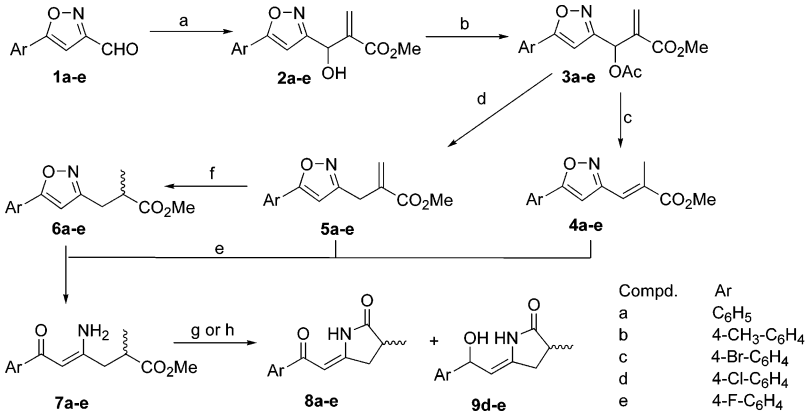
SCHEME 1[a]

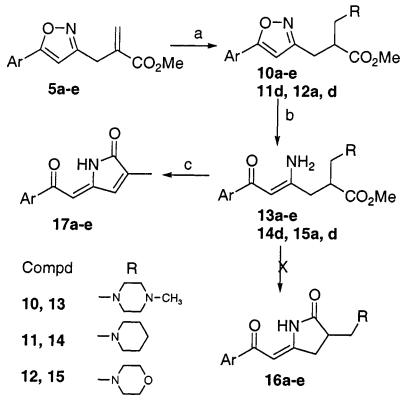


[a] Reagents and conditions: (a) CH_2=$CHCO_2Me$, DABCO, 10 min, rt. (b) AcCl, pyridine, CH_2Cl_2, 0 °C to rt, 3 h. (c) $NaBH_4$, MeOH, 2 h, rt. (d) DABCO, $NaBH_4$, THF:H_2O, 15 min, rt. (e) Raney-Ni, H_2, 30 psi, 2 h, rt. (f) 10% Pd/C, H_2, 30 psi, 3 h, rt. (g) NaH, toluene, 10 min, rt or DBU, THF, 30 min, rt. (h) 24 h at rt followed by a silica gel column.

5a−**e**) for the present study is outlined in Scheme 1. The substituted 3-isoxazolecarbaldehydes (**1a**−**e**) were subjected to Baylis−Hillman reaction to afford adducts **2a**−**e** in excellent yields. Subsequent acetylation of adducts **2a**−**e** furnished the acetates **3a**−**e**, which reacted with sodium borohydride under different reaction conditions to afford products **4a**−**e** and **5a**−**e**.[17,18] These substrates (**4a**−**e** or **5a**−**e)** were subjected to hydrogenolysis in the presence of Raney-Ni to yield enaminones **7a**−**e**, which on overnight storage at room temperature yielded a mixture of compounds based on the TLC analysis. Purification by column chromatography on silica gel led to isolation of a less polar product as compared to the enaminone **7a**−**e**. This product was assigned the structure **8a**−**e**. The stereochemistry across the exocyclic double bond in compounds **8a**−**e** was assigned as *Z* on the basis of NOE experiments. In a subsequent attempt to obtain the optimal yields of 2-pyrrolidinones (**8a**−**e**) through a one-pot procedure, the hydrogenation reaction was carried out under different conditions and even allowed to continue for longer periods, but the attempts were unsuccessful. Interestingly however, if the hydrogenation was run for long durations then two products were isolated during chromatography. The major component was the 2-pyrrolidinone (**8d**−**e**) while the minor polar product was identified as the hydroxy derivative (**9d**−**e**). The failure of the enaminones **7a**−**e** to cyclize upon hydrogenation may be due to poor nucleophilicity of the eneamine and therefore it was desired to identify an appropriate base to facilitate the cyclization procedure. It was found that the enaminones **7a**−**e** upon reaction with a catalytic amount of NaH in toluene at room temperature almost instantaneously yielded the desired cyclized derivatives (**8a**−**e**) in good yields. In addition, DBU was also found to be suitable to affect the cyclization though the reaction time was slightly higher.

A series of 3,5-susbstituted-2-pyrrolidinones were reported to be pharmacologically active compounds,[19] and

SCHEME 2[a]



[a] Reagents and conditions: (a) RH, MeOH, 8 h, rt. (b) Raney-Ni, H_2, 30 psi, 2 h, rt. (c) Silica gel column chromatography or rt for 48 h.

therefore it was considered that if the double bond in compounds **5a**−**e** was appropriately substituted, similar hydrogenation followed by ring closure of the resulting product should produce 2-pyrrolidinones with substitution at position-3 of the heterocyclic ring. To evaluate the feasibility of this approach, compounds **10a**−**e** were prepared by reacting compounds **5a**−**e** with *N*-methylpiperazine. These compounds (**10a**−**e**) were then subjected to hydrogenation in the presence of Raney-Ni (Scheme 2).

The hydrogenations furnished enaminones **13a**−**e** (on the basis of the polarity of spot on the TLC and ^{1}H NMR analysis of the crude product) but during purification on a silica gel column, these compounds completely transformed to yield a less-polar derivative compared to the enaminone. On the basis of spectroscopic evidence the structure of these compounds was identified as 1,5-dihydro-2-pyrrolones (**17a**−**e**) instead of the expected products **16a**−**e**. It was also observed that if these hydrogenation products were allowed to stand at room temperature for 48 h, then also the 1,5-dihydro-2-

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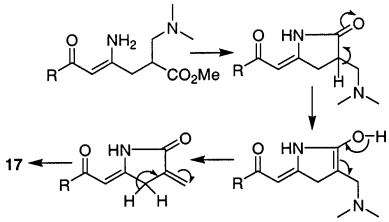
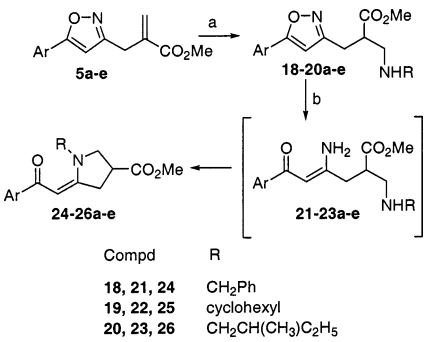


FIGURE 1. Mechanism for the formation of 1,5-dihydro-2-pyrrolones.

SCHEME 3[a]



[a] Reagents and conditions: (a) RNH_2, MeOH, 8 h, rt. (b) Raney-Ni, H_2, 30 psi, 3 h, rt.

pyrrolone derivatives were obtained in good yields. Similarly to compounds **7a**−**e** these compounds (**13a**−**e**) too, upon treatment with NaH, are cyclized to afford the products **17a**−**e** within a short period. The stereochemistry across the exocyclic double bond was assigned as *Z* on the basis of results of the NOE experiments. Similar to compounds **10a**−**e**, derivatives **11d**−**12a**,**d** led to the formation of 1,5-dihydro-2-pyrrolone rather than the desired products. The formation of the 1,5-dihydro-2-pyrrolone is explained on the basis of deamination as shown in Figure 1.

Mechanistic considerations generated interest in studying the fate of ring closure reactions in amino derivatives **18**−**20**, which were easily obtained from compound **5a**−**e** (Scheme 3). Interestingly the hydrogenolysis of compounds **18**−**20a**−**e** in the presence of Raney-Ni gave pyrrolidines **24**−**26a**−**e** instead of the expected enaminones **21**−**23a**−**e**. The stereochemistry across the exocyclic double bond was assigned as *Z*. These results therefore indicated that the elimination of a secondary base was favored in ring closure of enaminones **13**−**15** but elimination of ammonia was favored in the ring closure reactions of compounds **18**−**20** (Figure 2).

Since compounds **4a**−**e** led to 2-pyrrolidinones (**8a**−**e**), we envisioned that the amino derivatives **27** and **29** could be utilized for obtaining 1,5-dihydro-2-pyrrolone (**17**) and the pyrrolidines (**24**−**26**) thereby reducing the number of synthetic steps involved in the synthesis of these heterocycles. Thus in a model study compounds **27a** and **29b** were generated and subjected to hydrogenolysis in the presence of Raney-Ni. As expected, compounds **27a** and **29b** afforded the corresponding compounds **17a** and **24b**, respectively, in good yields (Scheme 4).

In conclusion, the present study reveals easy access to substituted 2-pyrrolidinones, 1,5-dihydro-2-pyrrolones, and *N*-substituted pyrrolidine derivatives. The synthetic

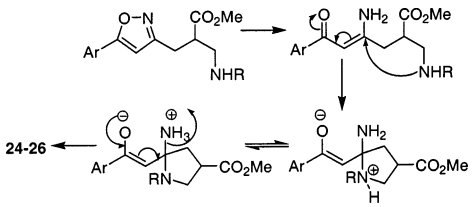
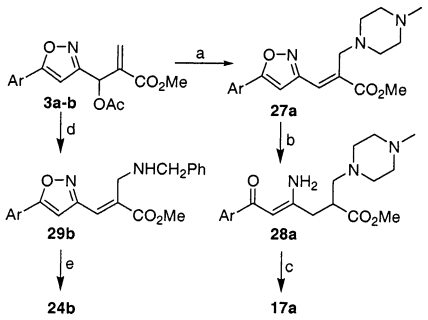


FIGURE 2. Mechanism for the formation of pyrrolidines.

SCHEME 4[a]



[a] Reagents and conditions: (a) *N*-methylpiperazine, MeOH, 8 h, rt. (b) Raney-Ni, H_2, 30 psi, 3 h, rt. (c) 24 h at rt followed by silica gel chromatography. (d) $PhCH_2NH_2$, MeOH, 8 h, rt. (e) Raney-Ni, H_2, 30 psi, 3 h, rt.

protocol described in this paper is simple and convenient, involves the use of inexpensive reagents, and is amenable to parallel synthesis. The facile nucleophilic substitution of amines in the Baylis−Hillman derivatives provides the opportunity to easily obtain the desired substitution on the heterocyclic nitrogen atom in the *N*-substituted pyrrolidine derivatives.

Experimental Section

General Considerations. See the Supporting Information.

General Procedure for Compounds 2a−e. See ref 13c.

General Procedure for Compounds 3a−e As Exemplified for 3b. To the stirred solution of compound **2b** (0.89 g, 3.25 mmol) in dry dichloromethane (5 mL) was added pyridine (0.48 mL, 6.0 mmol) followed by dropwise addition of a solution of acetyl chloride (0.46 mL, 6.5 mmol) in dry dichloromethane (3 mL) at 0 °C. After the addition was complete, the reaction was continued at room temperature for 3 h. The reaction mixture was extracted with dichloromethane (2 × 25 mL) and water (40 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to obtain an oily residue. The residue was purified through column chromatography over silica gel with hexane:ethyl acetate (85:15, v/v) as eluent to obtain 0.88 g (86%) of **3b** as a white solid.

2-[Acetoxy-(5-*p*-tolylisoxazol-3-yl)methyl]acrylic acid methyl ester (3b): mp 86−88 °C; ν_{max} (KBr) 1706 (CO_2Me), 1742 (OCOMe) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.17 (s, 3H), 2.39 (s, 3H), 3.78 (s, 3H), 6.06 (d, 1H, J = 0.74 Hz), 6.48 (s, 1H), 6.53 (s, 1H), 6.84 (s, 1H), 7.25 (d, 2H, J = 8.0 Hz), 7.64 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 21.2, 52.6, 66.55, 99.1, 126.2, 127.5, 128.2, 129.4, 130.7, 137.3, 141.1, 162.6, 165.3, 169.6, 170.8; mass (ES^+) *m/z* 338.33 (M^+ + Na). Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75, H, 5.43, N, 4.44. Found: C, 65.02, H, 5.33, N, 4.57.

General Procedure for Compounds 4a−e As Exemplified for 4d. To the solution of **3d** (1.34 g, 4.0 mmol) in methanol (5 mL) was added $NaBH_4$ (0.76 g, 8.0 mmol) with stirring at 0−5 °C. After 15 min the reaction was decomposed with water and extracted with ethyl acetate (2 × 30 mL). The organic phase was separated and washed with brine (40 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue upon column chroma-

tography over silica gel with hexane:ethyl acetate (85:15, v/v) furnished 0.85 g (77%) of pure **4d** as a white solid.

3-[5-(4-Chlorophenyl)isoxazol-3-yl]-2-methylacrylic acid methyl ester (4d): mp 153−154 °C; ν_{max} (KBr) 1712 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.29 (s, 3H), 3.85 (s, 3H), 6.64 (s, 1H), 7.46 (d, 2H, J = 8.6 Hz), 7.52 (d, 1H, J = 1.4 Hz), 7.74 (m, 2H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 15.4, 52.8, 72.7, 101.0, 125.6, 127.5, 129.8, 135.1, 136.9, 160.3, 168.4, 169.4; mass (ES^+) m/z 278.56 ($M^+ + 1$). Anal. Calcd for $C_{14}H_{12}ClNO_3$: C, 60.55, H, 4.36, N, 5.04. Found: C, 60.45, H, 4.49, N, 5.36.

General Procedure for Compounds 5a−e As Exemplified for 5e. To the solution of acetate **3e** (0.64 g, 2.0 mmol) in THF:water (3 mL, 1:1, v/v) was added DABCO (0.22 g, 2.0 mmol) and the reaction was allowed to proceed at room temperature. As soon as the solution became clear (ca. 15 min), $NaBH_4$ (0.08 g, 2.0 mmol) was added with stirring. The reaction was complete in 15 min, after which the reaction mixture was extracted with ethyl acetate (2 × 30 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated to obtain a residue that after chromatography on silica gel with hexane:ethyl acetate (90:10, v/v) as eluent afforded 0.43 g (83%) of **5e** as pale yellow oil (approximately as in ref 18).

2-[5-(4-Fluorophenyl)isoxazol-3-ylmethyl]acrylic acid methyl ester (5e): ν_{max} (neat) 1722 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.74 (s, 2H), 3.79 (s, 3H), 5.75 (d, 1H, J = 1.0 Hz), 6.35 (s, 2H), 6.36 (s, 1H, CH), 7.09−7.17 (m, 2H), 7.70, 7.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 29.2, 52.5, 99.7, 116.7, 128.3, 128.2, 136.9, 162.7, 166.6, 167.1, 169.3; mass (ES^+) m/z 262.33 ($M^+ + 1$), 284.60 ($M^+ + Na$). Anal. Calcd for $C_{14}H_{12}FNO_3$: C, 64.36, H, 4.63, N, 5.36. Found: C, 64.74, H, 4.66, N, 5.44.

General Procedure for Compounds 6a−e. See ref 16.

General Procedure for the Hydrogenation in the Presence of Raney-Ni As Exemplified for 24c. A mixture of compound **18c** (0.85 g, 2.0 mmol) and Raney-Ni (100 mg in ethanol) in methanol (10 mL) was subjected to hydrogenation in the Parr assembly at 35 psi at room temperature. The reaction was allowed to continue for 3 h. Thereafter, the catalyst was removed by vacuum filtering the reaction mixture through a Celite bed with methanol. The filtrate was evaporated to obtain an oily residue, which was taken up in ethyl acetate (2 × 20 mL) and washed with water (20 mL). The organic layers were pooled and dried over anhydrous Na_2SO_4 and the solvent was evaporated in vacuo to obtain the crude oil. Purification of the crude product by column chromatography over silica gel with hexane:ethyl acetate (60:40, v/v) as the eluent furnished 0.54 g (65%) of **24c** as a white solid.

1-Benzyl-5-[2-(4-bromophenyl)-2-oxoethylidene]pyrrolidine-3-carboxylic acid methyl ester (24c): mp 95−98 °C; ν_{max} (KBr) 1736 (C=O and CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.26−3.30 (m, 1H), 3.62−3.84 (m, 7H), 4.53 (s, 2H), 5.91 (s, 1H), 7.23−7.41 (m, 7H), 7.78−7.83 (m, 2H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 37.8, 39.4, 50.7, 52.7, 54.7, 87.8, 127.7, 128.3, 128.5, 129.4, 130.9, 131.6, 135.5, 141.9, 165.2, 173.9, 188.6; mass (FAB^+) m/z 336 ($M^+ + 1 - Br$). Anal. Calcd for $C_{21}H_{20}BrNO_3$: C, 60.88, H, 4.87, N, 3.38. Found: C, 60.70, H, 5.20, N, 3.66.

General Procedure for the Cyclization in the Presence of NaH As Exemplified for 8a. To the stirred suspension of NaH (0.0345 g in 60% oil, 1.5 mmol) in anhydrous toluene (2 mL) was added a solution of compound **7a** (0.37 g, 1.5 mmol) in toluene (5 mL) at ambient temperature. After 10 min the reaction mixture was quenched with water and extracted with ethyl acetate (15 mL). The organic layer was dried over Na_2SO_4 and evaporated to obtain a residue that was subjected to column chromatography over silica gel to yield 0.31 g (96%) of **8a** as a white solid.

3-Methyl-5-(2-oxo-2-phenylethylidene)pyrrolidin-2-one (8a): mp 162−163 °C; ν_{max} (KBr) 1650 (CONH), 1737 (C=O), 3450 (br, NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.34 (d, 3H, J = 7.1 Hz), 2.55−2.75 (m, 2H), 3.16−3.25 (m, 1H), 6.18 (s, 1H), 7.42−7.57 (m, 3H), 7.87−7.98 (m, 2H), 11.01 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 16.9, 34.1, 35.7, 95.6, 128.1, 129.8, 132.3, 132.7, 159.1, 181.5, 190.7; mass (ES^+) m/z 216.47 ($M^+ + 1$), 248.60 ($M^+ + Na$). Anal. Calcd for $C_{13}H_{13}NO_2$: C, C, 72.54; H, 6.09; N, 6.51. Found: C, 72.59, H, 5.83, N, 6.54.

General Procedure for the Cyclization in the Presence of DBU As Exemplified for 8b. To the stirred solution of **7b** (0.52 g, 2.0 mmol) was added DBU (0.36 mL, 2.4 mmol) and the reaction mixture was continued at ambient temperature. After completion (30 min) the reaction mixture was extracted with ethyl acetate (25 mL) and water (20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated to afford crude product, which was purified through column chromatography over silica gel. Elution with hexane:ethyl acetate (85:15, v/v) yielded 0.43 g (95%) of product **8b** as a white solid.

3-Methyl-5-(2-oxo-2-*p*-tolylethylidene)pyrrolidin-2-one (8b): mp 156−158 °C; ν_{max} (KBr) 1655 (CONH), 1736 (C=O), 3429 (br, NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.33 (d, 3H, J = 7.1 Hz), 2.41 (s, 3H), 2.53−2.74 (m, 2H), 3.13−3.21 (m, 1H), 6.17 (s, 1H), 7.25 (d, 2H, J = 8.0 Hz), 7.82 (d, 2H, J = 8.0 Hz), 10.93 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 16.9, 21.9, 34.1, 35.7, 95.6, 128.3, 129.6, 136.3, 143.8, 158.6, 181.5, 190.4; mass (ES^+) m/z 230 ($M^+ + 1$). Anal. Calcd for $C_{14}H_{15}NO_2 \cdot H_2O$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.88; H, 7.11; N, 5.70.

General Procedure for the Reaction of Amines As Exemplified for 10a. To the solution of compound **5a** (1.33 g, 5.0 mmol) in methanol (4 mL) was added the desired *N*-methylpiperazine (0.67 mL, 6.0 mmol) and the mixture was stirred at room temperature from 14 to 20 h (preferentially overnight). On completion, the excess solvent was evaporated and the residue was filtered from a small band of basic alumina with chloroform or chloroform:methanol (99.5:0.5, v/v). The eluent was evaporated to obtain 1.45 g (78%) of amine as a pale yellow oil (approximately as in ref 18).

2-(4-Methylpiperazin-1-ylmethyl)-3-(5-phenylisoxazol-3-yl)propionic acid methyl ester (10a): ν_{max} (neat) 1734 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.27 (s, 3H), 2.30−2.76 (m, 10H), 2.98−3.10 (m, 3H), 3.69 (s, 3H), 6.36 (s, 1H), 7.42−7.48 (m, 3H), 7.72−7.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ 27.2, 43.3, 46.2, 52.2, 53.4, 55.4, 60.1, 99.9, 126.2, 127.9, 129.3, 130.5, 162.6, 170.2, 175.1; mass (ES^+) m/z 344 ($M^+ + 1$). Anal. Calcd for $C_{19}H_{25}NO_3 \cdot H_2O$: C, 63.14; H, 7.53; N, 11.63. Found: C, 62.91; H, 7.33; N, 11.66.

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Supporting Information Available: General experimental information and spectroscopic details for all compounds, ^1H NMR spectra for compounds **3b**,**d**, **4d**, **5b**,**d**, **6e**, **7e**, **8b**,**d**, **10a**,**d**−**e**, **11d**, **12a**,**d**, **17d**,**e**, **18b**,**c**,**e**, **19b**,**c**,**d**−**e**, **20a**,**c**,**e**, **24a**−**e**, **25a**,**d**−**e**, **26a**,**d**−**e**, **27a**, **29b**, ^{13}C NMR spectra for **8b**,**d**, **10a**, **24b**,**c**,**e**, **25a**,**e**, **26a**,**e**, and mass spectra of **8b**, **10e**, **12a**, **18c**,**e**, **19e**, **20a**,**c**,**e**, **24c**, **25a**,**d**−**e,** and **26a**,**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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